REMARKS

The Office Communication of May 21, 2003, has been received and reviewed. Claims 1, 5, 6, 9-15, 28, 29 and 37-47 are pending. Claims 5, 6, 9-15, 28, 29 and 37-39 have been canceled without prejudice or disclaimer. New claims 40-66 have been added. Claims 1, 5, 6, 9-15, 28, 29 and 37-39 stand rejected under 35 U.S.C. § 112, first paragraph, as allegedly lacking enablement commensurate with the scope of the claims. In addition, claims 1, 5, 6, 9-15, 28, 29 and 37-39 stand rejected under 35 U.S.C. § 112, first paragraph, as allegedly lacking sufficient written description. All amendments are made without prejudice or disclaimer. Applicants respectfully request reconsideration and withdrawal of the rejections.

Support for claim amendments:

Support for claims 40-55 can be found throughout the specification. For example, the applicants have added new claims 40-55, which recite "a substance capable of activating the glucocorticoid receptor." Substances capable of activating the glucocorticoid receptor are disclosed throughout the specification, for example, at paragraphs 6, 18, 30, 34, 35 and 38 of the specification, which disclose glucocorticoids and analogue drugs such as dexamethasone as substances capable of activating the glucocorticoid receptor. Specifically, paragraph 38 teaches the glucocorticoid receptor antagonist RU486 as an antagonist of dexamethasone activation of the glucocorticoid receptor.

Support for claim 56 can be found throughout the specification, for example, at paragraphs 18 and 27. Paragraph 18 recites: "a method for preparing a pharmaceutical composition for reducing an unwanted T-cell response in a host, comprising culturing peripheral blood monocytes from the host to differentiate into dendritic cells, activating said dendritic cells in the presence of a glucocorticoid hormone and loading the activated dendritic cells with an antigen against which the T-cell response is to be reduced." Paragraph 27 recites "a pharmaceutical composition comprising a dendritic cell." Therefore, because at least paragraphs 18 and 27 provides *in haec verba* support for claim 56, no written description issue is raised by this claim (*see* MPEP § 2163.02).

Support for claim 57 can be found throughout the specification, for example, at paragraph 5, which states that dexamethasone is an example of a glucocorticoid ("the present invention shows that GC [glucocorticoids], such as [for example][1] dexamethasone"). In addition, the Merck Index (Therapeutic Category of "Glucocorticoid" in The Merck Index, thirteenth edition, pp. THER-24 (provided herewith)) and other references discussed herein and made of record, list "glucocorticoids", including the example of dexamethasone.

Support for claim 58 can be found throughout the specification, for example, at paragraphs 18 and 43. Paragraph 18 describes, *inter alia*, a method for preparing a pharmaceutical composition for reducing an unwanted T-cell response in a host, comprising culturing peripheral blood monocytes from the host to differentiate into dendritic cells, activating said dendritic cells in the presence of a glucocorticoid hormone and loading the activated dendritic cells with an antigen against which the T-cell response is to be reduced." Paragraph 43 describes, *inter alia*, loading dendritic cells with hsp65 and peptide p3-13, which are recognized by "Hsp65 specific T-cells."

Support for claim 59 can be found throughout the specification, for example, at paragraph 35, which describes "an allogeneic MLR [mixed lymphocyte reaction]." Further support can be found, *inter alia*, at paragraph 42.

Support for claim 60 can be found throughout the specification, for example, at paragraph 35, which describes "an allogeneic MLR [mixed lymphocyte reaction] ... [with] the addition of DEX [dexamethasone]."

Support for claim 61 can be found throughout the specification, for example, at paragraphs 18 and 35. Paragraph 18 is described herein and paragraph 35 describes "an allogeneic [allogenic] MLR [mixed lymphocyte reaction] ... [with] the addition of DEX [dexamethasone]," respectively.[2]

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[1] The common meaning of "such as" and "for example" is illustrated in the MPEP at § 2173.05(d).

[2] Glucocorticoid and glucocorticoid hormone represent alternative ways of referencing the same class of molecules. For example, see AHFS DRUG INFORMATION 91, 1810 (American Society of Hospital Pharmacists, Inc. 1991); and REMINGTON'S PHARMACEUTICAL SCIENCES 958-972 (Mack Publishing Co., 1985) both describing corticosteroids as

Support for claim 62 can be found throughout the specification, for example, at paragraph 18, which is described herein. Paragraph 18 describes a host at risk of a host versus graft disease and loading the dendritic cells with an antigen against which the T-cell respose is to be induced, which includes the antigens derived from grafts and transplantations (typically allogeneic antigens).

Support for claim 63, can be found throughout the specification, for example, at paragraph 21, which describes activation of dendritic cells through triggering of the CD40 receptor can involve either incubation with a CD8-CD40L fusion protein, a trimeric form of CD40L consisting of CD40L-molecules to which a modified leucine zipper has been attached, anti-CD40 antibodies, or cells that express CD40L.

Support for claim 64 can be found throughout the specification, for example, at paragraphs 18, 28, 35 and 43. Paragraph 18 is described herein and paragraph 28 states, *inter alia*, that the "dendritic cell and/or the functionally modified T-cell or precursors thereof are derived from an HLA-matched donor." Paragraph 43 describes, *inter alia*, "HLA-DR-matched DEX-treated immature DC." Paragraph 35 provides, *inter alia*, a working example supporting the claim.

Thus, support for claims 56-64 can be found throughout the specification. Moreover, although no requirement exists for *in haec verba* support (MPEP § 2163.02), the specification provides *in haec verba* support for at least claims 56-64. Therefore, the applicants submit that no written description issue(s) is/are raised by these claims.

Support for claims 65-68 can be found throughout the specification. For example, at paragraphs 18, 21, 28, 29, 31, 34 and 35. Activation of dendritic cells, for example, by administration of a glucocorticoid and/or forms of CD40L are disclosed throughout the specification.

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hormones and listing, *inter alia*, dexamethasone as an example of the glucocorticoid class.

Alleged lack of enablement:

Claims 1, 5, 6, 9-15, 28, 29 and 37-39 stand rejected under 35 U.S.C. § 112, first paragraph, as allegedly lacking enablement commensurate with the scope of the claims. Claims 5, 6, 9-15, 28, 29 and 37-39 have been canceled. To the extent that the rejection applies to claim 40-68, the applicants respectfully traverse the rejection.

The Office states that the specification "does not reasonably provide enablement for, *in vivo* or *in vitro* induction of non- responsiveness of polyclonal T cells to any undefined antigen or the *in vivo* induction of non-responsiveness when an 'unwanted T-cell response' is ongoing" (emphasis added; page 2 of Paper 15). The applicants respectfully submit that the Office Action appears to indirectly put forward the position that the *in vitro* data of the specification does not support claims to *in vivo* uses.[3] The applicants have described how the invention functions using *in vitro* working examples. However, the Office acknowledges enablement of only *in vitro* use of the invention. The applicants respectfully submit that the specification is enabling for both *in vitro* and *in vivo* induction of non-responsiveness of polyclonal T cells.[4] As the Office bears the burden of presenting reasons for the lack of an enabling correlation between *in vitro* and *in vivo* results, in the absence of any such reasoning, the applicants assume that no challenge to the

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[3] The applicants submit that a requirement for *in vivo* data to support *in vivo* use is contrary to established law (*see* MPEP § 2164.02, citing *In re Brana*, 51 F.3d 1560, 1566, 34 USPQ2d 1436, 1441 (Fed Cir. 1995); Fujikawa v. Wattanasin, 93 F.3d 1559, 1565-1566, 39 USPQ.2d (BNA) 1895 (Fed. Cir. 1996)). A copy of Fujikawa v. Wattanasin is submitted herewith.

[4] The Office Actions, while rejecting the claims for an alleged lack of written description seem to the applicants to be directed to enablement of glucocorticoids other than dexamethasone. Cronstein *et al.*, (1992) A Mechanism for the Anitiinflammatory Effects of Corticosteroids: The Glucocorticoid Receptor Regulates Leukocyte Adhesion to Endothelial Cells and Expression of Endothelial-leukocyte Adhesion Molecule 1 and Intercellular Adhesion Molecule 1, *Proc. Nat. Acad. Sci. U.S.A.* 89:9991-9995) (submitted herewith) shows the use of dexamethasone and references comparison to the weaker glucocorticoid, cortisol, as an example of glucocorticoids. The authors of this paper conclude that "antagonism by dexamethasone ... is a specific instance of the general biological principle that the glucocorticoid receptor is a hormone-dependent regulator of transcription" (Cronstein *et al.*, summary). Cronstein *et al.* recognize that the results that they obtained with the example dexamethasone are applicable to the entire glucocorticoid class. Likewise, the applicants used dexamethasone as a representative of all glucocorticoids and apply those results to glucocorticoids in general. In the absence of reasoning why results obtained with dexamethasone would not be applicable to glucocorticoids in general, the applicants submit that the data enables all glucocorticoids and that the express word "glucocorticoids" provides adequate written description of "glucocorticoids."

correlation of the *in vitro* data to use *in vivo* is intended. Thus, the applicants submit that the *in vitro* data provided in the specification supports and enables *in vivo* use of the claimed compositions. Furthermore, the applicants respectfully submit that the *in vitro/in vivo* correlation is firmly established by the executed declaration, submitted herewith.

The Office states that the current rejection is based on two key factors (page 3 of Paper 15). First, the Office alleges that "the specification fails to disclose precisely how the antigens that induce unwanted T cell responses are established". *Id.* Second, the Office alleges that "given that the claims are drawn to a method for preparing a pharmaceutical composition, the specification fails to adequately disclose that the DCs [dendritic cells] prepared with these unknown antigens would function as a pharmaceutical composition *in vivo*."[5] *Id.*

The applicants submit that exactly this last question is answered in the previously unexecuted declaration, which is now executed. The examples provided in the declaration demonstrate unequivocally the use of the alternatively stimulated dendritic cells as a pharmaceutical composition *in vivo* (page 3 of Paper 15). The alternatively activated dendritic cells are capable of inducing a prolonged skin graft survival when administered as a pharmaceutical composition *in vivo* to mice having undergone a skin graft with an incompatible donor-recipient combination.

Figures 5a and 5b of the declaration show a striking difference in skin graft survival. In Figure 5a the administered dendritic cells are of the same type C57BL/6 (H-2^b) as the graft (*i.e.*, carrying and displaying the same antigens), demonstrating that alternatively activated dendritic cells displaying antigens identical to the antigens displayed on the graft cells are capable of tolerizing a subject and result in prolonged (about doubled) graft survival. The Examiner alleges that no antigen loaded DCs were used in the disclosed experiments. The applicants would again like to stress that the activated antigen presenting dendritic cells in this experiment do display antigens. In particular, the dendritic cells present the same antigens as the skin graft cells, which

[5] If the Office intends this statement to constitute reasons for a lack of an enabling correlation between the *in vitro* data disclosing a mechanism of the invention and *in vivo* use, the applicants respectfully submit that the declaration submitted herewith establishes the correlation.

are also of C57BL/6 (H-2^b) origin, thereby inducing tolerization to these antigens (*see also*, Hancock *et al.*, 1996). The recipient/host mice are of a different type, BALB/c (H-2^d), than the donor and therefore will normally immunologically react to the allogeneic C57BL/6 graft. *Id.* Thus, dendritic cells loaded with C57BL/6, type H-2^b, antigens, function as a pharmaceutical composition *in vivo*, as described in the specification, and the specification teaches a person of ordinary skill in the art how the antigens that induce unwanted T cell responses are established (*e.g.*, graft derived).

In Figure 5b, a different skin graft was used (DBA/1 (H-2^q) origin). Indeed, here the C57BL/6-antigen displaying C57BL/6 dendritic cells (the graft and dendritic cells are not syngeneic[6]) were ineffective in prolonging the survival of the DBA/1 graft (*i.e.*, no tolerization of the graft was observed). Thus, Figure 5a illustrates the effectiveness of the claimed method and *in vivo* function of the invention, as described in the specification, confirming the *in vivo* applicability of the applicants' *in vitro* tests (for example, Example 4). Figure 5b illustrates the specificity of the claimed method.

The Office asserts that no antigen-loaded DCs were used in the disclosed experiments [of the declaration]. Hancock *et al.* (1996), Costimulatory function and expression of CD40 ligand, CD80, and CD86 in vascularized murine cardiac allograft rejection., *Proc. Natl. Acad. Sci. U S A.* 93(24):13967-13972, describes graft versus host rejection with C57BL/6 (H-2b) and BALB/c (H-2d) mice through CD40L binding. As will be noted by review of Hancock *et al.*, the authors of the reference do not list the source or identity of all of the antigens, other than by reference to the particular mice (for example, C57BL/6 (H-2^b) and BALB/c (H-2^d), page 13967, second column), but simply refer to allograft[7] rejection (for example, Figures 1-3 and Table 2). Thus, Hancock *et al.* presumes that a person of ordinary skill in the art would recognize the source of

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[6] A Dictionary of Genetics, 1997, defines syngeneic as "pertaining to genetically identical organisms such as identical twins or the members of a highly inbred strain. Because syngenic animals have the same antigens on their tissues, they can exchange skin or organ grafts successfully." (A copy is enclosed herewith.)

[7] KING AND STANSFIELD, A DICTIONARY OF GENETICS 14 (5th ed., Oxford University Press 1997) defines allograft as "a graft of tissue from a donor of one genotype to a host of a different genotype but of the same species." (A copy is enclosed herewith.)

the antigens (the allogeneic[8] mice). Likewise, the declaration does not expressly state the source of the antigens. The source of the antigens is presented in the form of a description of the allogeneic mice C57BL/6 (H-2^b) and BALB/c (H-2^d).

An advantage of the invention is that the exact identity of all possible antigens is not required. Therefore, the invention is not limited to the use of any specific antigen. A person of ordinary skill in the art would recognize that professional antigen presenting cells (APCs)[9], such as dendritic cells, can be loaded with any antigen for which tolerization is desired (*i.e.*, the unwanted immune response). Antigens will be taken up, processed and displayed by MHC class I and II molecules on the surface of the APC to surrounding T-cells (Kampgen *et al.* (1991), Class II Major Histocompatibility Complex Molecules of Murine Dendritic Cells: Synthesis, Sialylation of Invariant Chain, and Antigen Processing Capacity are Down-Regulated Upon Culture. *Proc. Natl. Acad. Sci. U S A.* 88(8):3014-3018 (discussing the abundant antigen presentation by dendritic cells through MCH molecules)).[10] Thus, loading of an antigen may be accomplished by bringing dendritic cells into contact with any antigen source for which tolerization is desired, ranging from its own internal proteins (as in Figure 5 of the declaration; Hancock *et al.*, 1996; and Kampgen *et al.*, 1991) or external sources, such as, purified peptides, proteins or cell extracts from grafts/transplants (for example, as in paragraphs 35 and 43 of the specification). In Example 5 of the declaration, the dendritic cells are syngeneic (*i.e.*, of the exact same origin and genetic make-up as the graft cells), hence expressing, or loaded with, antigens identical to the graft/transplant antigens.

Furthermore, antigens for specific diseases are known in the art. For example, multiple sclerosis is a demyelinization disease, associated with an autoimmune response to the myelin

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[8] The On-line Medical Dictionary defines allogeneic as "[t]wo or more individuals (or strains) are stated to be allogeneic to one another when the genes at one or more loci are not identical in sequence in each organism." A DICTIONARY OF GENETICS 14, defines "allogeneic graft" as "a graft of tissue between genetically different members of the same species, especially with regard to alloantigens (*q.v.*)." (Copies of each reference are enclosed herewith.)

[9] Antigen presenting cells (APC) are cells derived from bone marrow and comprise a heterogeneous set of cells, including dendritic cells in lymphoid organs, Langerhans cells in skin, and certain types of macrophages, which present antigens on MHC glycoproteins. BRUCE ALBERTS *ET AL.*, MOLECULAR BIOLOGYY OF THE CELL (2nd ed. Garland Publishing, Inc., 1989) pp. 1044-1057, 1045.

basic protein. Nicholson *et al.* disclose alterations of an antigen and states that "Much of the experimental work in models of autoimmunity has focused on the immune response to specific peptide ligands (cognate ligands)."[11] In addition, Greten *et al.* disclose that "many HLA-A2-restricted antigens have been identified for human ... autoimmune diseases, and cancer."[12] Finally, Stemme *et al.* disclose autoantigens derived from oxLDL as being of potentially "significant pathogenetic importance in atherosclerosis."[13] Thus, the selection of an antigen for a specific disease is known in the art.

As explained herein, specific antigens are not expressly listed in the disclosure, as the invention is not limited to any specific antigen. In practice, when tolerizing a subject for grafts or transplants it is not even feasible to point out a single specific antigen, as there are typically many reactive antigens. As exemplified in the declaration, for example, Figure 5, an entire spectrum of antigens derived from a graft/transplant can be displayed on alternatively activated dendritic cells according to the current invention. There simply is no need, nor is it desirable, to select a single antigen in order to reduce an unwanted immune response. Further, the antigens will depend on the genetic make-up of the host (HLA type). Thus, the specification provides the only possible enabling description of the antigens (for example, paragraph 7 of the specification, indicating "that such DC [dendritic cells] loaded with appropriate antigens can be exploited as a novel approach for specifically down regulating unwanted T-cell responses *in vivo*.") (emphasis added). Further, specific antigens, be they multiple antigens from an allogeneic graft or transplant or specific antigens such as the myelin basic protein, are known in the art.

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[10] Kampgen *et al.*, like Cronstein *et al.*, does not specifically list all possible antigens present in a cell.

[11] Nicholson *et al.* (1998) Heteroclitic Proliferative Responses and Changes in Cytokine Profile Induced by Altered Peptides: Implications for Autoimmunity *Proc. Natl. Acad. Sci. U.S.A.* 95:264-269, 264. A copy of this reference is submitted herewith.

[12] Greten *et al.*, (1998) Direct Visualization of Antige-specific T Cells: HTLV-1 Tax11-19-specific $CD8^+$ T Cells are Activated in Peripheral Blood and Accumulate in Cerebrospinal Fluid From HAM/TSP Patients, *Proc. Natl. Acad. Sci. U.S.A.* 95:7568-7573, 7572. A copy of this reference is submitted herewith.

[13] Stemme *et al.* (1995) T Lymphocytes from human Atherosclerosis Plaques Recognize Oxidized Low Density Lipoprotein, *Proc. Natl. Acad. Sci. U.S.A.* 92:3893-3897, 3897. A copy of this reference is submitted herewith.

Therefore, the specification does disclose, in the only feasible way, precisely how the antigens that induce unwanted T cell responses are established (page 3 of Paper 15). In addition, the specification describes a mechanism of the invention using *in vitro* data which correlates and enables use *in vivo*. Thus, a person of ordinary skill in the art, who would recognize the source of the antigens from the description in the specification, is enabled to practice the invention *in vitro* and ***in vivo***.

For these reasons and reasons made of record previously, the applicants respectfully submit that the specification enables a person of ordinary skill in the art to use "the DCs [dendritic cells] prepared with these unknown antigens ... as a pharmaceutical composition *in vivo*" and provides an enabling disclosure of "how the antigens that induce unwanted T cell responses are established" (page 3 of Paper 15). Reconsideration and withdrawal of the rejection is respectfully requested.

Alleged lack of written description:

Claims 1, 5, 6, 9-15, 28, 29 and 37-39 stand rejected under 35 U.S.C. § 112, first paragraph, as allegedly lacking sufficient written description. Claims 5, 6, 9-15, 28, 29 and 37-39 have been canceled. To the extent that the rejection applies to claim 40-68, the applicants respectfully traverse the rejection.

The Office asserts "that an obvious corollary would be that adequate written description does not extend to subject matter which is not disclosed, but would be obvious over what is disclosed" (page 4 of Paper 15). The applicants respectfully disagree with the premise of the asserted corollary. In particular, the standard for determining compliance with the written description requirement is an objective standard wherein "an applicant must convey with reasonable clarity to those skilled in the art that ... he or she was in possession of the invention ...." (MPEP § 2163.02; emphasis added). A person of ordinary skill in the art has a knowledge of the art, which the applicants do not need to reiterate in the specification. "[A] patent specification is not intended nor required to be a production specification." (MPEP § 2165.01). Therefore, the applicants are not required to provide *in haec verba* support for those aspects of

the invention known by a person of ordinary skill in the art at the time of filing (MPEP § 2163.02). The specification need only convey with reasonable clarity to those skilled in the art possession of the invention. Thus, that which is alleged by the Office to be "obvious over what is disclosed," would necessarily provide a reasonable written description, understood by a person of ordinary skill in the art as demonstrating possession of the invention as of the filing date. As a result, the applicants submit that the corollary is not consistent with applicable law and that the specification provides sufficient written description of glucocorticoids as a class.[14]

"A description as filed is presumed to be adequate, unless or until sufficient evidence or reasoning to the contrary has been presented by the examiner to rebut the presumption" (MPEP § 2163.04). In this case, the only evidence presented is an "obvious corollary" to the law. Since the Office has not satisfied its burden, the applicants respectfully request reconsideration and withdrawal of the rejection.

The Office asserts that insufficient written description exists to show possession of a "means for reducing IL-12p40 production by said dendritic cell .... the specification fails to disclose an adequate written description or a representative number of species to describe the claimed genus." (page 4 of Paper 15). The applicants submit that the specification has disclosed means for reducing IL-12p40 production by the dendritic cells. For example, paragraph 34 discloses the reduction in IL-12p40 production. Thus, the specification provides a written description for a means of reducing IL-12p40 production and a means of causing dendritic cells to secrete IL-10 *in vitro*.[15]

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[14] The Office acknowledges that the members of the class are obvious in light of the applicants' specification. "It would seem that an obvious corollary would be that adequate written description does not extend to subject matter which is not disclosed [presumably, an express listing of all glucocorticoids], but would be obvious over what is expressly disclosed" (page 4 of Paper 15). Further, as described herein, glucocorticoids are frequently described by reference to effects produced by one or a few representatives, and the specification expressly, and repeatedly, provides *in haec verba* support for "glucocorticoids."

[15] Under 35 U.S.C. § 112, paragraph six, "[a]n element in a claim for a combination may be expressed as a means or step for performing a specified function without the recital of structure, material, or acts in support thereof, and such claim shall be construed to cover the corresponding structure, material, or acts described in the specification and equivalents thereof."

The rejection appears to the applicants to require a written description of every, or at least a large number of representative examples of, member of the phrases at issue. The applicants respectfully submit that an adequate written description imposes no such requirement. "An applicant shows possession of the claimed invention by describing the claimed invention with all of its limitations using such descriptive means as words, structures, figures, diagrams, and formulations that fully set forth the claimed invention," MPEP §2163, citing *Lockwood v. American Airlines, Inc.*, 107 F.3d 1565, 1572, 41 USPQ2d 1961, 1966 (Fed. Cir. 1997) and *Amgen, Inc. v. Chugai Pharmaceutical*, 927 F.2d 1200, 1206, 18 U.S.P.Q.2d 1016, 1021 (Fed. Cir. 1991) ("one must define a compound by 'whatever characteristics sufficiently distinguish it'"). The applicants respectfully submit that the specification complies with the written description requirements. Nevertheless, the applicants have amended the claims to recite the phrase "a substance capable of activating the glucocorticoid receptor" of which glucocorticoid hormones and analogue drugs such as dexamethasone are species clearly described throughout the specification (for example, paragraphs 30 and 38) or "glucocorticoid hormones".

The Office has previously rejected claims containing "glucocorticoids" as lacking sufficient written description (page 3 of Paper 13). Specifically, "It is the Examiner's position that a 'general discussion or definition is insufficient to specifically describe a claimed invention. ...'" The applicants respectfully submit that the Examiner's position is inconsistent with established law. A general discussion or definition may define a compound sufficiently to distinguish it. The "general discussion" provided in the present specification fully conveys with reasonable clarity to those skilled in the art that the applicants were in possession of the invention.[16] The applicants have amended claims 1, 5, 6, 9-15, 28, 29 and 37-39 to recite "a substance capable of activating the glucocorticoid receptor" in another attempt to find a phrase

[16] The specification defines glucocorticoids by their known attributes, by reference to an art accepted representative and by the mechanism of action. In addition to the references cited herein, Remmington's compares at least the following members of the glucocorticoids: Bethamethasone is compared to dexamethasone and cortisol; dexamethasone to cortisol; and paramethasone acetate with cortisone (Remmington's at 963, 965 and 969, respectively). Thus, the similarities between members of the glucocorticoid class are known in the art and a person of ordinary skill in the art is able to substitute another glucocorticoid for dexamethasone.

acceptable to the Examiner. The applicants submit that glucocorticoids, which are substances capable of activating the glucocorticoid receptor are supported by an adequate written description.

As discussed herein, a person of ordinary skill in the art would recognize dexamethasone as an example of a glucocorticoid receptor agonist and a substance capable of activating the glucocorticoid receptor. The applicants have demonstrated the function of the invention using a representative of the glucocorticoids, dexamethansone, and the art recognized similarities between members. For example, paragraph 5 of the specification expressly describes dexamethasone as an example of a glucocorticoid ("GC [glucocorticoids], such as [for example] dexamethasone").

Beyond the applicants' express statement that dexamethasone is an example of a glucocorticoid[17] (for example, paragraphs 5, 6 and 7 of the specification), a person of ordinary skill in the art would recognize that the applicants were in possession of, and described substances capable of activating a glucocorticoid receptor. For example, a search of the PubMed database for "glucocorticoid" and "dexamethasone" produces over 14,000 hits, with over 300 full text articles available online (printouts showing the respective search results are submitted herewith). One of the over 14,000 PubMed papers (Cronstein *et al.*, (1992) A Mechanism for the Anitiinflammatory Effects of Corticosteroids: The Glucocorticoid Receptor Regulates Leukocyte Adhesion to Endothelial Cells and Expression of Endothelial-leukocyte Adhesion Molecule 1 and Intercellular Adhesion Molecule 1, *Proc. Nat. Acad. Sci. U.S.A.* 89:9991-9995) is submitted herewith. This reference shows the use of dexamethasone and reference to the less potent steroid receptor agonist cortisol as an example of glucocorticoids and using this example the authors of the paper conclude that antagonism by dexamethasone ... is a specific instance of the general biological principle that the glucocorticoid receptor is a hormone-dependent regulator of transcription." (Cronstein *et al.* 1992 at 9991, first column). Thus, as far back as 1992 dexamethasone was recognized as an example of a substance capable of activating a

[17] Glucocorticoids are substances capable of activating the glucocorticoid receptor, as would be recognized by a

glucocorticoid receptor. The reference uses dexamethasone as a representative of glucocorticoids in general, demonstrating the art recognized relationship among glucocorticoids. Therefore, even assuming for the sake of argument that the specification provides only a general written description of substances capable of activating the glucocorticoid receptor (glucocorticoids) by way of art recognized dexamethasone, the applicants submit that a sufficient written description of glucocorticoids is provided.

Moreover, AHFS DRUG INFORMATION 91, 1991; and REMINGTON'S PHARMACEUTICAL SCIENCES 958-972 (Mack Publishing Co., 1985) both describe corticosteroids as hormones and list, *inter alia*, dexamethasone as an example of the glucocorticoid class.[18] Again, demonstrating recognition by a person of ordinary skill in the art that dexamethasone is an example of a glucocorticoid.[19] Finally, the document entitled "Glucocorticoids Disease Mechanism II: Inflammation" (provided herewith) expressly states that "[c]ommon glucocorticoids include prednisone, dexamethasone, and hydrocortisone." Therefore, the applicants have provided written description for glucocorticoids and substances that activate glucocorticoid receptors (*e.g.*, glucocorticoid hormones and analogue drugs) to sufficiently describe the claimed genus.

The Office maintains the argument that of the claimed antigen genus, no species are disclosed (page 4 of Paper 15). The applicants again presume that the Office is asserting a lack of written description for the term "antigen," since the specification does not expressly list every possible antigen. The applicants respectfully submit that such an express list is not required and would pose a burden that would be impossible to satisfy.

As explained herein, specific antigens are not expressly listed in the disclosure, as the invention is not limited to any specific antigen and antigens are known in the art (*see* Nicholson *et al.*, 1998; and Stemme *et al.*, 1995). The invention may be used in combination with any

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person of ordinary skill in the art.

[18] *See also,* Therapeutic Category of "Glucocorticoid," as shown in THE MERCK INDEX, (13th ed., 2001), pp. THER-24, (listing over 60 glucocorticoids, including dexamethasone), which are substances capable of activating a glucocorticoid receptor.

[19] *See* FN 10 glucocorticoids and glucocorticoid hormones, which are substances capable of activating a glucocorticoid receptor.

antigen which causes an unwanted immune response that the subject needs to be tolerized for. Any antigen that can be presented by a dendritic cell, for example, on its MHC class I or class II molecules, may be used. Bringing a culture of dendritic cells into contact with the antigen for which the T-cell response is to be reduced (as claimed in claim 1) is sufficient for dendritic cells to take up, process and display the antigen. In practice, when tolerizing a subject for grafts or transplants it is not feasible to point out all of the many potentially reactive antigens. Essentially, a complete list of antigens would necessitate a disclosure of every allele, now carried or to be carried, of every gene product in a species to be covered by a claim. As exemplified in the declaration, for example, Figure 5, an entire spectrum of antigens derived from an allogeneic graft/transplant can be displayed on alternatively activated dendritic cells according to the current invention. There simply is no need, nor is it desirable, to select a single antigen in order to reduce an unwanted immune response. As will be recognized by a person of ordinary skill in the art, in most instances the unwanted immune response will be determined by several antigens, not by one specific antigen. Further, the antigens will depend on the genetic make-up of the host (HLA type), for example, the allogeneic graft source, which represent allelic differences between C57BL/6 (H-2^b) and BALB/c (H-2^d) mice. Thus, the specification provides the only feasible written description of the antigens, which are known in the art, (for example, paragraph 7 of the specification, indicating "that such DC loaded with appropriate antigens can be exploited as a novel approach for specifically down regulating unwanted T-cell responses *in vivo*.") (emphasis added). Thus, the applicants have provided an adequate written description of all of the antigens that will function in the present invention, clearly appraising a person of ordinary skill in the art that the inventors were in possession of the invention at the time of filing.

The applicants also note that limiting the claims to merely dexamethasone would leave the current invention without meaningful protection. Any skilled artisan, using the guidance of the applicant's specification, would be readily able to select a different substance capable of acting on the glucocorticoid receptor. Many glucocorticoids are known in the art, all of which will be, depending on the choice and concentration, sufficiently effective for modulating

dendritic cell response. In addition, any subject not previously treated and described in the specification would present antigens not expressly described in the specification.

Reconsideration and withdrawal of the rejection is respectfully requested.

CONCLUSION

In the event questions remain after consideration of these remarks and amendments, the Office is kindly requested to contact applicant's attorney at the number given below.

Respectfully submitted,

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Date: November 21, 2003
GSD/gsd

Enclosures:

Petition for extension of time under 37 C.F.R. § 1.136(a);
Executed Declaration under 37 C.F.R. § 1.132;
AHFS DRUG INFORMATION 91;
REMINGTON'S PHARMACEUTICAL SCIENCES;
Fujikawa v. Wattanasin;
Dictionary of Genetics;
Cronstein *et al.*, 1992;
Hancock *et al.*, 1996;
Kampgen *et al.*, 1991;
Nicholson *et al.*, 1998;
Greten *et al.*, 1998;
Stemme *et al.*, 1995; and
Cell, 1985.